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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/647,544	10/26/2000	Evy Lundgren-Akerlund	003300-685	8350

21839 7590 04/14/2004

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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 04/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/647,544	LUNDGREN-AKERLUND, EVY	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21,23-31,33-46,48-86,88-99,101-108 and 110-137* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,23-25,76 and 126* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/22/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 12/22/03, is acknowledged.

2. Claims 1-21, 23-31, 33-46, 48-86, 88-99, 101-108, and 110-137 are pending.

3. Claims 2-21, 26-31, 33-46, 48-75, 77-86, 88-99, 101-108, 110-125 and 127-137 stand withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

4. Claims 1, 23-25, 76 and 126 are under consideration in the instant application as they read on an recombinant or isolated collagen binding integrin subunit α10 comprising the amino acids of SEQ ID NO:2 and the amino acids sequence from about amino acids No. 140 to about amino acid No. 137 of SEQ ID NO:2.

5. It is noted that New Grounds of objection is set forth herein.

6. The amendment filed 12/22/03 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

The phrase "incorporated by reference" to International Application No. PCT/SE99/00544 and the Swedish Patent Application Nos. 9801164-6 and 9900319-6 on page 1 of the specification does not enjoy the status as part of the original disclosure in the application because the phrase "incorporated by reference" is not referred to in specification as originally filed.

7. In view of the amendment filed on 12/22/03, only the following rejections are remained.

8. Claims 1, 24-25 and 126 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 1 is indefinite in the citation of "same biological activity". It is unclear what biological activities are claimed and the metes and bounds of such biological activity is undefined.

Applicant's arguments, filed 12/22/03, have been fully considered, but have not been found convincing.

Applicant argues that the specification provides the skilled artisan with the definition of "same biological activities". Applicant points out that the specification provides discussion as to the specific biological activities of the integrin subunit α10, and the sequences comprising same.

Page 7 of the specification recites specific biological activities such as binding to markers, targeting of cells or tissues expressing the integrin subunit α10. Page 10 of the specification discusses binding entities which bind the integrin subunit a10, as well as homologs or fragments thereof. Thus, the skilled artisan would be clearly apprised as to what is meant by "same biological activities".

However, the integrin subunit α10 biological activity is poorly known at the time the invention was made. The skilled artisan would not know which biological activity is being claimed.

b. Claims 24-25 are indefinite for reciting "from about amino acid No." in lines 2-3. It is unclear how many amino acids constitute "about". One of skill in the art would not know if applicant meant with "about", is it exactly the recited amino acids, or 4 amino acids less, as many as 11 amino acids less, or even more.

Applicant's arguments, filed 12/22/03, have been fully considered, but have not been found convincing.

Applicant submits that the meaning of "about" as recited in claims 24-25 would be clear to the skilled artisan, as this word is commonly recited in similar context in many issued patents and is well-accepted.

It is well settled that whether similar claims have been allowed to others is immaterial. See In re Giolito, 530 F.2d 397, 188 USPQ 645 (CCPA 1976) and Ex parte Balzarini 21 USPQ2d 1892, 1897 (BPAI 1991). Moreover, as stated In re Borkowski, 505 F2d 713,718,184 USPQ29,33 (CCPA 1974), "The Paten Office must have the flexibility to reconside and correct prior decisions that may find to have been in error". In a similar context, the court in Fessenden v.Coe, 38 USPQ 516,521 (CADC 1938) stated that '[t]wo wrongs cannot make a right."

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1, 23-25, 76 and 126 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the same reasons set forth in the previous Office Action mailed 9/22/03.

Applicant's arguments, filed 12/22/03, have been fully considered, but have not been found convincing.

Applicant argues regarding fragments and homologues that undue experimentation would not be required to determine appropriate fragments or homologues. Further, Applicant submits the specification defined homologues as "essentially the same molecules form other species", while the Oxford Dictionary of Biochemistry and Molecular Biology defined homolog as "of proteins from different species having identical or similar functions". Applicant submits that it is well known in the art that different integrins and subunits thereof are not homologues to each other. Thus, they are not interchangeable with each other. Integrin a subunits share an overall identify of only 20-40%.

However, the specification does not appear to have provided sufficient guidance as to which subsequences of SEQ ID NO:2 would share the same biological activity. Neither does the specification appear to have provided any working examples of any functional subsequences. Thus it would require undue experimentation of the skilled artisan to determine which subsequences of SEQ ID NO:2 would have the function of the full length molecule.

The specification discloses only one species, yet claim any protein with a sequence essentially the same or homologues thereof. It is noted that the specification does not define "essentially". How is one to determine whether a given polypeptide or a fragment of that polypeptide which is essentially the same as SEQ ID NO:2 is a derivative of α10 integrin subunit or another member of the integrin family? No active fragments, homologues, derivatives, etc. have been provided, and the claims cannot be considered enabled for anything other than human α10 of SEQ ID NO: 1 or the fragments: SEQ ID NO:7, aa 952-986 of SEQ ID NO:2, or aa 140-337 of SEQ ID NO:2.

Applicant argues that because the sequence for human α10, and its fragment are disclosed in the present specification, Applicants submit that undue experimentation would not be required for the skilled artisan to practice the present invention. Undue experimentation would not be required for the skilled artisan to locate appropriate fragments or homologues because these techniques (such as hybridization techniques, RT-PCT techniques, immunoprecipitation and immunoblots) are well known in the art. Further, Applicant argues that using what is provided in the specification with these well known techniques would only require basic experimentation on the part of the skilled artisan, rather than undue experimentation.

However, the claims fail to meet the enablement requirement for the "how to make and use" prongs of the U.S.C 112, 1st paragraph. The instant fact pattern fails to indicate that a representative number of homologues molecule is disclosed. The artisan would not know the identity of a reasonable number of representative homologues falling within the scope of the instant claim and consequently would not have known how to make them. In order to satisfy the U.S.C 112, 1st paragraph, the specification has to teach how to make and use the invention, not how to identify the invention. Until the time when such homologues of SEQ ID NO: 2 identity polypeptides are found, then one skill in the art can make them.

With respect to which specific amino acid sequences are essential, which amino acid residues are most tolerant to modification and which must be conserved, Applicant submits that the skilled

artisan would be able to locate recognizable domains of the integrins within each of the four collagen binding integrins using sequence alignments α10, αl, and α2 (see Appendix A, showing sequence alignment of four collagen binding integrins α10, α11, αl and α2). Applicant contends that the deduced amino acid sequences from αl, α2, α10, and α11 have been compared and it was found that those recognizable domains that are conserved between the four integrins. Even before the present application was filed, sequence alignments of α10, αl and α2 were easily performed by the skilled artisan without undue experimentation. Thus, Applicants submit it would be clear to the skilled artisan as to which specific amino acids sequences are essential, which amino acid residues are most tolerant to modification and which must be conserved.

Applicant is relying upon certain biological activities and the disclosure of a single species to support an entire genus. The claims as written encompass a broad genus of polypeptides with an unlimited number of possibilities with regard to the length of the polypeptide sequence. Further, the enablement issues of making the protein still remain because the specification does not teach and provide sufficient guidance as to which amino acid of SEQ ID NO: 2 would have been altered such that the resultant polypeptide would have retained the claimed biological activity. In addition, a collagen binding integrin subunit α10 fragments provides a range of activities, not all which are necessarily predictive of promoting adhesion. Therefore, absent the ability to predict which of these fragments would function as claimed, and given the lack of data on regions critical for activity, for one of skill in the art to practice the invention as claimed would require a level of experimentation that is excessive and undue.

With respect to use of SEQ ID NO: 2 as a marker or target in transplantation of cartilage or chondrocytes, Applicant draws the Examiner's attention to Appendix B and C. APPENDIX B depicts primary human chondrocytes may be identified by using anti-alpha10beta1 antibody. "cells" were identified in FACS by use of a mAb against integrin alpha10beta1 (mAb produced from knowledge of the sequence of the I-domain of the integrin alpha1beta1) (APPENDIC B). APPENDIX C depicts a population of cells (mesenchymal stem cells" may be identified by use of the mAb against α10 (mAb produced from knowlededge of the sequence of the I-domain of the integrin alpha1beta1) from a mixed population of hMNCs. Regarding Lehnert et al. Applicant's position is that there may not be a correlation between mRNA expression and protein expression.

However, Applicant appears to use antibodies against α1β1 integrin receptor wherein the antibodies crossreact with the α10 I-domain base on epitope sequence homology. Since no anti-alpha1 antibodies were used as a control, the skilled artisan would not know whether the marker is α1 or α10 subunit. Further, it is unclear what type of cells were used in APPENDIX B. As for the APPENDIX C, given that Articular chondrocytes are the only cells that express α10 subunit, then the results just confirm that hypothesis. However, such a test is not indicative that α10 is restricted to chondrocytes because other cells such as those mentioned in Lehnert et al are not among the cell population tested. Further, the specification on pages 25-26, under example 11 discloses that immunohistochemical staining of α10 in fascia around tendon and skeletal muscle

and in tendon structures in heart valves. Therefore, it is unclear whether α10 expression profile is restricted to chondrocytes in cartilage tissues or can also be found in other tissues such as ossification groove of Ranvier, muscle epimysium, tendon/ligament sheath, aortic and atrioventricular valves of the heart.

The issue of the claimed vaccine has not been address by the Applicant.

11. Claims 1, 23-25, 76 and 126 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the same reasons set forth in the previous Office Action mailed 9/22/03.

Applicant's arguments, filed 12/22/03, have been fully considered, but have not been found convincing.

Applicant is in possession of a recombinant or isolated collagen binding integrin subunit α10 comprising that amino acid of SEQ ID NO:2 or fragment of SEQ ID NO:10, wherein fragment is SEQ ID NO:7, aa 952-986 of SEQ ID NO:2, or aa 140-337 of SEQ ID NO:2.

Applicant is not in possession of any recombinant or isolated collagen binding integrin subunit α10 comprising essentially the amino acid sequence shown in SEQ ID NO:2, or homologues or Fragments thereof having essentially the same biological activity in claim 1; any fragment of the integrin subunit a10, wherein the fragment is the amino acid sequence from about amino acid No. 952 to about amino acid No. 986 of SEQ ID NO: 2 in claim 24; any fragment of the integrin subunit a10, wherein the fragment is the amino acid sequence from about amino acid No. 140 to about amino acid No. 337 of SEQ ID NO: 2 in claim 25; vaccine comprising the subunit α10, or a homologue or fragment of said integrin or subunit α10, wherein the fragment is selected from the group consisting of the cytoplasmic domain, the I-domain and the spliced domain in claim 76 or the integrin subunit a10 of SEQ ID NO:2 , wherein the integrin subunit α10 is a marker or target in transplantation of cartilage or chondrocytes in claim 126.

Applicant describes an ELISA assay to test the functionality of the I-domain of the α10β1. Applicant points to APPENDIX D which shows the results from ELISA assay. APPENDIX D shows that alpha10 I-domain bound to collagen type II and that the binding is dependent on divalent cations (Mg^{2+}). Applicant submits that such results demonstrated that the α10 I-domain has a function that is similar to the intact integrin α-chain.

However, the Examiner notes that the claimed invention which is drawn to a genus may be adequately described if there is a (1) sufficient description of a representative number of species, or (2) by disclosure of relevant, identifying characteristics sufficient to describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize

applicant was in possession of the claimed invention. To satisfy the disclosure of a "representative number of species" will depend on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. "Relevant, identifying characteristics" include structure or other physical and /or chemical properties, functional characteristics coupled with a known or disclosed correlation between function and structure, or a combination of such identifying characteristics sufficient to show the applicant was in possession of the claimed genus. (see Revised Guidelines for the Examination of Patent Applications Under the 35 U.S.C.112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No.4, pages 1099-1111, Friday January 5, 2001).

In the instant case, however, there is no described or art-recognized correlation or relationship between the structure of the invention, α10 and it's biological activity, the feature deemed essential to the instant invention. Therefore, one of skill in the art would not envisage, based on the instant disclosure, the claimed genus of homologues and fragments of αl0, wherein the homologues/fragments having essentially the same biological activity of SEQ ID NO:02 which retain the features essential to the instant invention.

"it is not sufficient to define the recombinant molecule by its principal biological activity, e.g. having essentially the same biological activity, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property." Colbert V. Lofdahl, 21 USPQ2d, 1068, 1071 (BPAI 1992).

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 1 and 126 stand rejected under 35 U.S.C. 102(b) as being anticipated by Takada et al (IDS Ref No. 6).

Takada et al teach a human α3 subunit, an integrin receptor for collagen (see abstract in particular). Takada et al further teach a nine amino acid sequence of metal binding domains general structure (DX(D/N)X(D/N)GXXD)) (see abstract in particular) fragment. SEQ ID NO:2 has three fragments of the metal binding structure at positions (aa 490-502, DTDRDGTTD, aa 558-566, DLNQDGFAD and aa 619-628, DLDGDDLVD). These metal binding domains have the same biological function in referenced α3 and claimed SEQ ID NO: 2.

While the prior art teachings may be silent as to the "a marker or target in transplantation of cartilage or chondrocytes" per se; the product the reference is the same as the claimed product.

Therefore "a marker or target in transplantation of cartilage or chondrocytes" is considered inherent properties.

The reference teachings anticipate the claimed invention.

Applicant's arguments, filed 12/22/03, have been fully considered, but have not been found convincing.

Applicant submits that Takada et al is not related to the α-10 integrin subunit, neither suggests nor discloses anything that will lead the skilled artisan to the existence of this subunit. Applicant submits that nothing in the reference to lead the skilled artisan to use the new subunit α10 according to the claimed [methods] products. Applicant contends that Takada et al., disclose the cloning and isolation of the a-3 subunit of human α3-β1.

However, Takada et al teaches fragments that are 100% identical to amino acid residues of SEQ ID NO:2 (α10) that have essentially the same biological activity (i.e. metal binding domains). Because the reference fragments are the same as the claimed fragments, being a "marker or target in transplantation of cartilage or chondrocytes" is considered inherent properties of the claimed fragments.

14. No claim is allowed.

15. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maher Haddad, Ph.D.
Patent Examiner
April 9, 2004

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
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Continuation of Disposition of Claims: Claims withdrawn from consideration are 2-21,26-31,33-46,48-75, 77-86,88-99,101-108,110-125 and 127-137.